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EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,484	RIDDER ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *1-32 and 40-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/8/04;6/15/06;* 7/21/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: MeSH database search

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group III (claims 33-40) without traverse in the reply filed on July 21, 2006 is acknowledged. Applicants' further election of p16 INK4a (claim 34), EpCam (claim 35), and EpCam (claim 39) with traverse is also acknowledged.

The traversal is on the grounds that: 1) claim 33 is a linking claim, 2) there should not be a restriction between p16INK4a and p14ARF, 3) there should not be a restriction requirement among the cyclin dependent kinase inhibitors (p16INK4a, p19, p21, and p27), and 4) there should not be a restriction requirement between cytoskeleton proteins.

Applicant's traversal is unpersuasive for the following reasons:

1) Claim 33 does not constitute a proper linking claim. The proteins listed in claim 34 such as Cyclin dependent kinase inhibitors and minichromosome maintenance proteins (Mcm) 2–7, constitute an improper Markush group since the members of the Markush group ordinarily must belong to a recognized physical or chemical class or to an art-recognized class, see MPEP 803.02.

2) The proteins listed in claims 34 and 35 are separate and distinct for the reasons of record provided in the previous Office Action. While a search of the prior art for one Group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources even if the Groups were placed in the same class and subclass.

2. Claims 1-51 are pending.

Claims 1-32, and 41-51, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 33-40 are examined on the merits.

Oath/Declaration

3. The Oath/Declaration is objected to since an Inventor, Mattias Herkert, did not place the date next to his signature.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 33-40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 33 is vague and indefinite for the recitation of "cervical cancer and their respective *precursor* stages." It is unclear what stages are included and what stages

are regarded as precursor. For example, normal cervical epithelium could constitute a precursor stage. Accordingly, the metes and bounds of the claimed invention cannot be determined.

b. Claim 33 recites the limitation "the sample solution" in line 9. There is insufficient antecedent basis for this limitation in the claim.

c. Claim 33 is vague and indefinite. The preamble of claim 33 states "a method for diagnosing cervical dysplasia, cervical cancer" in claim 33. However, the method steps read on diagnosing only cervical dysplasia in line 10. It is not clear if "cervical dysplasia, cervical cancer" is one cervical disorder or if the cervical dysplasia is separate and distinct from cervical cancer.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 33-39 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of diagnosing cervical dysplasia by preparing a sample solution from a human cervical sample and detecting the level of p16INK4a, does not reasonably provide enablement for a method of diagnosing cervical dysplasia by preparing a sample solution from a human cervical sample, detecting the

level of p16INK4a and detecting the level of EpCam, and normalizing the level of the relevant marker, p16INK4a, to the normalization marker, EpCam. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention and the breadth of the claims: Claim 33 is drawn to a method for diagnosing cervical dysplasia, cervical cancer and their respective precursor stages in human cervical body sample comprising preparing a sample solution from a human cervical sample, detecting the level of at least one relevant marker characteristic for the presence of cervical dysplasia, detecting the level of at least one normalization marker characteristic for the presence of epithelial cells, normalizing the levels of the

relevant markers to the levels of the normalization markers detected within the sample solution and diagnosing cervical dysplasia based on the normalized levels of the relevant markers to the normalization markers. Claims 34 and 35 are drawn to the method wherein one relevant marker is p16INK4a and one normal marker is EpCam. Claim 36 is drawn to the method wherein the method is used for early detection or primary screening tests of cervical lesions. Claim 37 is drawn to the method wherein said human cervical body sample is a swab, a secretion, an aspirate, a lavage, a cell, a tissue, a biopsy or a body fluid. Claim 38 is drawn to the method wherein epithelial cells are ectocervical or endocervical cells. Claim 39 is drawn to the method wherein the normalization marker is EpCam.

The state of the prior art and the level of predictability in the art: The prior art teaches that EpCam has variable expression in cervical squamous epithelial cells. Litvinov SV et al. (American Journal of Pathology 148(3), 865-875, 1996) teach that EpCam expression was sometimes observed in morphologically normal ectocervical tissue but only in areas bordering cervical intraepithelial neoplasia (CIN) lesions, see Abstract, lines 12-16. Litvinov et al. further teach that EpCam was regularly present during the early stages of neoplasia. A clear increase, not only in the number of EpCam expressing cells but also in levels of EpCam expression was observed during the progression from CIN I to CIN III, see Abstract, lines 25-28. Litvinov et al. teach that expression of EpCam in ectocervical lesions did not coincide with the reappearance of epithelial cytokeratins (CK8 and CK18), see Abstract, lines 28-31. Litvinov et al. conclude that the observed continuous expression of EpCam in the basal layers of

dysplastic lesions may itself be a factor contributing to the disturbances in normal differentiation processes in such lesions and EpCam may serve as a good marker for grading CINs as well as an early marker of dysplastic/neoplastic changes in cervical squamous epithelium, see page 872, right column, first full paragraph, lines 1-4; and page 874, left column, last paragraph, lines 4-8. Therefore, the use of a protein such as EpCam, with expression levels that vary during cancer progression, and may be a factor contributing to the disturbances in normal differentiation processes in cervical cancer lesions, as a marker for normalization would be considered unpredictable by one of ordinary skill in the art.

The amount of direction provided by the inventor and the existence of working examples: The specification does not provide adequate support for utilizing EpCam expression as a normalization marker for cervical dysplasia. In Example 5, the specification discloses that normalization is carried out by applying a threshold value obtained by measuring OD for the marker EpCam, see page 47, lines 12-14. Below a certain threshold (corresponding to 2000 columnar endocervical cells), the sample does not contain an adequate amount of endocervical cells, see page 47, lines 14 and 15. No guidance is provided as to the possible OD range for the obtained threshold value. The specification merely states that, "The value for the cells [as] well as for OD may vary depending to [sic] the reaction conditions", see page 47, lines 17 and 18. However, in view of the teachings of Litvinov, the level of expression of EpCam varies depending on stage and progression of cervical dysplasia. Therefore, it is unclear how EpCam could be used as a normalization marker.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed inventions without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support Applicants' claim to a method for diagnosing cervical dysplasia by normalizing the levels of relevant markers such as p16INK4a with EpCam. All of the factors considered in the sections above, underscores the criticality of providing working examples in the specification.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that a method for diagnosing cervical dysplasia by normalizing the levels of relevant markers such as p16INK4a with EpCam would require undue experimentation in order to use the invention as claimed by the Applicants.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 33, 34, and 36-38 are rejected under 35 U.S.C. §102(b) as being anticipated by Von Knebel Doeberitz et al. (U.S. Patent 6,709,832; §371 of PCT/DE99/020494 with an international publication date of January 13, 2000) as evidenced by the National Library of Medicine's MeSH database and Ranki et al. (Journal of Clinical Microbiology 28(9): 2076-2081, 1990).

Von Knebel Doeberitz et al. teach a method for the early diagnosis of cervical cancer by detecting the expression level a relevant marker, p16, characteristic for the presence of cervical dysplasia, see column 2, lines 11-14; column 3 and column 4, Example 1. p16 and p16INK4a are synonymous terms for the same protein as evidenced by the attached MeSH database search. Von Knebel Doeberitz et al. teach the body sample comprises biopsies, aspirates, urine, and blood, see column 2, lines 33-40. Von Knebel Doeberitz et al. teach cervical carcinomas, its preliminary stages such as cervical intraepithelial neoplasias (CINI-III) as well as carcinomas in situ (CIS). Von Knebel Doeberitz et al. further teach measuring the level of a marker, p16, in normal tissue as a control, see column 4, lines 44-47. According to the specification, the term normalization marker shall refer to marker molecules used for normalization purposes, see page 13, lines 23 and 24. It is the Examiner's position that comparing p16 expression in cervical cancer cells with p16 expression in normal cells constitutes a normalization control.

Cervical carcinomas would inherently include ectocervical and endocervical cells as evidenced by Ranki et al., see page 2076, Materials and Methods, Specimens, line 4 through page 2077, line 2.

Thus, the instant invention is anticipated by Von Knebel Doeberitz et al. as evidenced by the MeSH database and Ranki et al.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 33, 34, 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sano T et al. (American Journal of Pathology 153(6): 1741-1748, 1998), in view of O'Brien et al. (U.S. Patent 5,976,799, patent date November 2, 1999), the MeSH database and Ranki et al. (Journal of Clinical Microbiology 28(9): 2076-2081, 1990).

Sano et al. teach that marked overexpression of p16 protein was observed in all cervical cancers and preneoplastic lesions, see Abstract, lines 16-20 and page 1742, left column, Cell Lines and Tissue Specimens section. p16 and p16INK4a are synonymous terms for the same protein in view of the attached MeSH database search.

Ranki et al. teach that cervical carcinomas include ectocervical and endocervical cells, see page 2076, Materials and Methods, Specimens, line 4 through page 2077, line 2.

Sano et al. do not teach utilization of a second marker. This deficiency is made up for by the teachings of O'Brien et al.

O'Brien et al. teach a method for early detection of cancer using p16 gene products and a second marker, beta-tubulin, that appears at substantially the same level in both normal and tumor samples, see column 2, lines 9-12. O'Brien et al. further teach a calibrated chart wherein a second marker, beta tubulin gene product, serves as a calibration control, see column 2, lines 22-26.

It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to utilize the method of Sano et al. with a second protein marker of O'Brien et al. to obtain normalized expression levels of a relevant marker protein, p16INK4a, with a second marker to obtain a calibrated expression curve.

One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Sano et al. and O'Brien et al. since expression levels vary depending on the number of cells obtained in the test sample and since in order to compare expression between two samples, a control indicative of the total amount of protein or RNA present in the sample must also be utilized.

Thus, claims 33, 34, 36-38 are obvious over Sano et al. in view of O'Brien et al., the MeSH database, and Ranki et al.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 33, 34, 36-38, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/650,057 in view of the National Library of Medicine's MeSH database and Ranki et al. (Journal of Clinical Microbiology 28(9): 2076-2081, 1990).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons: claims 1-6 are drawn to a method for detecting cervical cancer by determining the overexpression of cyclin dependent kinase inhibitor p16, and setting up a threshold for detection by comparing p16 expression levels in a healthy cervical body sample. p16 and p16INK4a are synonymous terms for the same protein in view of the attached MeSH database search.

Ranki et al. teach that cervical carcinomas inherently include ectocervical and endocervical cells, see page 2076, Materials and Methods, Specimens, line 4 through page 2077, line 2.

The instant claims differ from those in Application '057 in that a second marker protein is utilized to normalize for the presence of epithelial cells instant of utilizing a sample from another subject. According to the specification, the term normalization marker shall refer to marker molecules used for normalization purposes, see page 13,

lines 23 and 24. It is the Examiner's position that comparing p16 expression in cervical cancer cells with p16 expression in normal cells constitutes a normalization control.

This is a provisional obviousness-type double patenting rejection.

14. Claims 33, 34, and 36-38, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,709,832 in view of the MeSH database and Ranki et al. (Journal of Clinical Microbiology 28(9): 2076-2081, 1990).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent and the application are claiming common subject matter, as follows: a method for detecting cervical cancer comprising determining the overexpression of p16 in a human cervical sample utilizing biopsies. p16 and p16INK4a are synonymous terms for the same protein as demonstrated by the attached MeSH database search. Ranki et al. teach that cervical carcinomas inherently include ectocervical and endocervical cells, see page 2076, Materials and Methods, Specimens, line 4 through page 2077, line 2.

According to the specification, the term normalization marker shall refer to marker molecules used for normalization purposes, see page 13, lines 23 and 24. It is the Examiner's position that comparing p16 expression in cervical cancer cells with p16 expression in normal cells constitutes a normalization control.

Conclusion

15. Claim 40 is objected to for depending on a rejected claim.

No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

David Humphrey, Ph.D.

August 29, 2006